UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/351,149	07/12/99	THORPE	P 4001.002/383

HM12/1107

SHELLEY P M FUSSEY
WILLIAMS MORGAN & AMERSON PC
7676 HILLMONT
SUITE 250
HOUSTON TX 77040

EXAMINER	
SHARAREH,S	
ART UNIT	**PAPER NUMBER**
1619	13

DATE MAILED: 11/07/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/351,149	Thorpe et al
Examiner	**Group Art Unit**
Shahnam Sharareh	1619

☒ Responsive to communication(s) filed on *Aug 7, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is clos d** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-32, 43, and 44* is/are pending in the applicat

Of the above, claim(s) *10-15, 20-23, and 44* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-9, 16-19, 24-32, and 43* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3,5,7,9*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Amendment filed on August 7, 2000 has been entered. Claims 33-42 are canceled. Claims 1-32, 43-44 are pending. Applicant's election without traverse of Group I Paper No. 11 is acknowledged. Applicant's election of amino phospholipid targeting agent, antibody or fragment thereof, a coagulant, and a second anti-cancer agent is acknowledged. Claims 1-9, 16-19, 24-32, 43 read on the elected species. Claims 10-15, 20-23, 44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species.

Priority

2. Acknowledgment is made of the priority of the instant application under Title 35, USC 119 (e) of the U.S. application Serial No. 60/092589, filed July 13, 1998, and U.S. application Serial No. 60/110600 filed on December 2, 1998. Thus, the effective priority date used for the examination of the instant application is March July 13, 1998.

Amino Acid Sequence Disclosure

Applicant's disclosure of nucleotide and/or amino acid sequences complies with the requirements of 37 CFR 1.821 through 1.825.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-9, 16-19, 24-32, 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. The recitation of "biologically effective amounts" is indefinite. It is not clear what constitute biologically effective amounts. More specifically, for what purpose is said "biologically effective amount" effective? The metes and bounds of the claim is not clear

4. Claim 43 rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the scope of the subject matter which applicant(s) regard as their invention. More specifically, it is not clear for what inventive category are applicants seeking protection? Applicant is required to clarify the limitation of the claim language. In the instant case, it is not apparent what constitutes "in combination"? Is the claimed invention directed to a method utilizing a combination of instant components? Is the claimed invention directed to a composition comprising the recited components? Is the claimed invention directed to a kit comprising the instant compounds? or is the claimed invention directed to an apparatus containing the instant elements? Applicant is encouraged to conform with USPTO practices in reciting claim limitations. A transitional phrase such as "comprising", "consisting essentially of" and "consisting of" define the scope of a claim with respect to what unrecited additional components or steps, if any, are excluded from the scope of the claim. In the instant case, the scope and thus the metes and bounds of the claim is not clear.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-9, 16-19, 24-32, 43 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim1-49 of U.S. Patent No. 6,036,955, claims 40-61 of U.S. Patent No. 6,051,230. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of both the instant claims and the patented claims overlap. In the instant case both set of claims are directed to kits comprising a at least one targeting agent-therapeutic agent directed to an amino phospholipid, and at least a second targeting agent-therapeutic agent specific to coagulation of the tumor vasculature by delivery of a coagulant.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-9, 16-19, 24-32, 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang et al, *Science* 275:547-550,1997 in view of Martin US Patent 6,043,094.

The instant claim is directed to combination of a targeting agent-therapeutic agent construct, a targeting agent-detectable agent construct and at least a second anti-cancer agent.

Huang et al disclose methods of occluding tumor vasculature in solid tumors of mice by targeting the cell surface domain of tumor vascular endothelial cells with a bispecific antibody-tissue factor conjugate, *abstract, page 549.* Huang et al specifically teach that adminsteration of a drug acting on the tumor cells and selective blood coagulation of tumor vasculature can improve efficacy of antivascular therapy of solid tumors, *page 549, 3rd col.* Huang, however, does not specifically disclose the coadministeration of a second cancer agent with his antibody-tissue factor conjugate.

Martin disclose liposome-based therapy for mammalian subjects comprising administering to the subject, liposomes with outer surfaces that contain an affinity moiety effective to bind specifically to a target surface at which the therapy is aimed, *abstract.* The liposomes of Martin entrap a therapeutic agent, wherein said agent is released when the liposome's affinity moiety is effectively bound to the specific site of interest such as solid tumor-specific antigen, *col 3 38-50, col 13 lines 44-46.* Martin's affinity moiety include a polysaccharide which binds to endothelial leukocyte adhesion molecules ("ELAM"), *col 4 lines 1-5, col 9 table 1.* Martin disclose various methods of forming his therapeutic-targeting construct, *col 15 lines 5-56.* Martin does not teach combination administration his therapeutic moieties with second cancer agent.

Haung et al and Martin disclose therapeutic methods by targeting specific endothelial cell surface markers of solid tumors, accordingly, their teachings are viewed to be in the same filed of endeavor.

Although, Huang et al do not specifically show the combination therapy of a solid tumor by administering an antibody-therapeutic agent conjugate with a second anticancer agent, they do

suggest that such combination could significantly improve the efficacy of coaguligand therapy, therefore, it would have been obvious to one of ordinary skill in the art at the time of invention to administer the antibody-coagulant conjugate of Huang et al with a second anti-cancer agent of Martin et al to enhance the antivascular therapy of a solid tumor of interest. Furthermore, preparing a convenient therapeutic kit for a clinical setting containing the essential components of such therapy would have been well within purview of an ordinary practitioner and thus obvious at the time of invention.

7. Claims 1-9, 16-19, 24-32, 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gimbrone et al US Patent 5,632,991 in view of Dvorak et al, *Cancer cells,* 1991: 3(3); 77-85.

Gimbrone discloses a targeting agent conjugated to an antibody directed to ELAM-1 (E-Selectin), *col 5, lines 18-38.* Gimbrone also disclose the use of his targeting agent-therapeutic agent conjugate, alone or in combination with the antibody or antibody fragment (a second anti-cancer agent), Finally, Gimbrone also disclose methods for detecting E-Selectin expression within the body of a patient comprising steps of detecting E-Selectin by labeling the E-Selectin antibody with a radioactive isotope that can be detected under a scintillation counter, *col 18, lines 60-65*. Finally, Gimbrone teach that various inflammatory cytokines such as TNF and IL-1 are able to induce the expression of ELAM-1. Gimbrone does not teach the combination therapy of the his antibody-therapeutic agent conjugate with a second anti-cancer drug.

Dvorak et al teach various strategies that would have possibly improved the delivery of monoclonal antibodies to tumor vasculature; one of which is to identify the antigen that is

uniquely expressed on tumor blood vessel endothelium, *see page 82.* Dvorak et al express that antibodies directed against such antigens may be linked to either metabolic poisons or to radioisotopic cytotoxics and would been expected to necrotize solid tumors by compromising their blood supply. Such teachings would have suggested to an ordinary skilled artisan how to enhance the targeting of the vascularized tumors. Dvorak has indicated that such approach offers additional advantages in that the antibodies employed need not be customized for a specific tumor, *see page 83*, thus providing a motivation to utilize antibodies that are directed to such antigenic sites in combination with other modalities with tumor therapy. Dvorak et al teach that the metabolic hyper permeability of tumor blood vessels in carcinomas act similar to proinflammatory mediators such as histamine in creating leaky blood vessels, *page 80*, and that is further analogous to the vascular hyperpermibility that occurs during the wound healing process. Thus, an ordinary routiner would have concluded that the endothelial cell layer of leaky blood vessels are capable of inducing a leukocyte mediated response. Dvorak et al, however, admit that there had been no antigens identified that would have been specific for tumor vessel endothelial surface.

Both Dvorak and Gimbrone teach methods of delivering targeted monoclonal antibody to neoplastic areas, thus, their teachings are viewed as being in the same field of endeavor.

Although Gimbrone et al do not fully teach the combination of his antibody-therapeutic agent conjugate, one would have been motivated at the time of invention to target ELAM-1 in the vasculature bed of solid tumors such as carcinomas, because as taught by Gimbrone the induced expression of such endothelial cell surface glycoprotein has been shown to be consistent with

other inflammatory processes that are mediated by leucocytes (such as neutrophils). Therefore, one ordinary skilled in the art would have had a reasonable expectation to succeed in improving images of vascularized tumor when administering the monoclonal antibody conjugates of Gimbrone et al which are conjugated to a therapeutic agent in combination with a chemotherapeutic agent as suggested by Dvorak, because the presence of ELAM-1 as a surface antigen on tumor blood vessel endothelium; as evident in other similar leucocyte mediated inflammatory processes, would have been expected. Finally, preparing a therapeutic kit to conduct such method would have also been obvious.

8. Claims 1-9, 16-19, 24-32, 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gimbrone et al US Patent 5,632,991 in view of Huang et al *Science* 275:547-550,1997.

The teachings of Gimbrone and Huang are discussed above. Huang provides motivation that coadminsteration of a drug action on the tumor cells themselves with a selective blood coagulation of tumor vasculature can improve efficacy of antivascular therapy of solid tumors, accordingly, one of ordinary skill in the art would have been motivated to coadminster the conjugates of Gimbrone and Huang to target a vascular site of solid tumor, because according to Huang he would have had a reasonable expectation to see improve results of his vascular tumor therapy. Respectively, preparing a therapeutic kit comprising the essential elements of such method would have also been obvious .

Conclusion

9. No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh, PharmD whose

telephone number is (703) 306-5400. The examiner can normally be reached on Monday to Friday from 8:30 a.m. to 5:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Diana Dudash can be reached on 703-308-2328. The fax phone number for this Group is 703-308-4556. Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is 703-308-1235.

ss 11/2/2000

DIANA DUDASH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600